FORM PTO-1390 (Modified) (REV 11-2000) U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE

TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371

ATTORNEY'S DOCKET NUMBER	U.S. APPLICATION NO. (IF KNOWN, SEE 37 CFR)
DVME-1015US	**09/913597**

INTERNATIONAL APPLICATION NO.	INTERNATIONAL FILING DATE	PRIORITY DATE CLAIMED
PCT/NL/00102	**17 February 2000**	**18 February 1999**

TITLE OF INVENTION

Method and Apparatus for Determining the Cardiac Output of a Patient

APPLICANT(S) FOR DO/EO/US

Jozef Reinier Cornelis JANSEN et al.

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. ☒ This is a **FIRST** submission of items concerning a filing under 35 U.S.C. 371.
2. ☐ This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. 371.
3. ☒ This is an express request to begin national examination procedures (35 U.S.C. 371(f)). The submission must include items (5), (6), (9) and (24) indicated below.
4. ☒ The US has been elected by the expiration of 19 months from the priority date (Article 31).
5. ☒ A copy of the International Application as filed (35 U.S.C. 371 (c) (2))
   a. ☐ is attached hereto (required only if not communicated by the International Bureau).
   b. ☒ has been communicated by the International Bureau.
   c. ☐ is not required, as the application was filed in the United States Receiving Office (RO/US).
6. ☐ An English language translation of the International Application as filed (35 U.S.C. 371(c)(2)).
   a. ☐ is attached hereto.
   b. ☐ has been previously submitted under 35 U.S.C. 154(d)(4).
7. ☒ Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371 (c)(3))
   a. ☐ are attached hereto (required only if not communicated by the International Bureau).
   b. ☐ have been communicated by the International Bureau.
   c. ☐ have not been made; however, the time limit for making such amendments has NOT expired.
   d. ☒ have not been made and will not be made.
8. ☐ An English language translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3)).
9. ☒ An oath or declaration of the inventor(s) (35 U.S.C. 371 (c)(4)).
10. ☐ An English language translation of the annexes of the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371 (c)(5)).
11. ☒ A copy of the International Preliminary Examination Report (PCT/IPEA/409).
12. ☒ A copy of the International Search Report (PCT/ISA/210).

Items 13 to 20 below concern document(s) or information included:

13. ☒ An Information Disclosure Statement under 37 CFR 1.97 and 1.98.
14. ☐ An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.
15. ☐ A **FIRST** preliminary amendment.
16. ☐ A **SECOND** or **SUBSEQUENT** preliminary amendment.
17. ☐ A substitute specification.
18. ☐ A change of power of attorney and/or address letter.
19. ☐ A computer-readable form of the sequence listing in accordance with PCT Rule 13ter.2 and 35 U.S.C. 1.821 - 1.825.
20. ☐ A second copy of the published international application under 35 U.S.C. 154(d)(4).
21. ☐ A second copy of the English language translation of the international application under 35 U.S.C. 154(d)(4).
22. ☐ Certificate of Mailing by Express Mail
23. ☒ Other items or information:

amended pages 2, 6-7, and 9-11 filed 7 March 2001 under Art. 34 PCT and annexed to the PCT/IPEA/409; and corrected pages 1-3 of the International Preliminary Examination Report dated 10 August 2001

U.S. APPLICATION NO. (IF KNOWN, SEE 37 CFR)	INTERNATIONAL APPLICATION NO	ATTORNEY'S DOCKET NUMBER
09/913597	PCT/NL/00102	DVME-1015US

24. The following fees are submitted:.		CALCULATIONS PTO USE ONLY	
BASIC NATIONAL FEE (37 CFR 1.492 (a) (1) - (5)) :			
☐ Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a)(2)) paid to USPTO and International Search Report not prepared by the EPO or JPO	**$1000.00**		
☒ International preliminary examination fee (37 CFR 1.482) not paid to USPTO but International Search Report prepared by the EPO or JPO	**$860.00**		
☐ International preliminary examination fee (37 CFR 1.482) not paid to USPTO but international search fee (37 CFR 1.445(a)(2)) paid to USPTO	**$710.00**		
☐ International preliminary examination fee (37 CFR 1.482) paid to USPTO but all claims did not satisfy provisions of PCT Article 33(1)-(4)	**$690.00**		
☐ International preliminary examination fee (37 CFR 1.482) paid to USPTO and all claims satisfied provisions of PCT Article 33(1)-(4)	**$100.00**		
ENTER APPROPRIATE BASIC FEE AMOUNT =		**$860.00**	
Surcharge of **$130.00** for furnishing the oath or declaration later than ☐ 20 ☐ 30 months from the earliest claimed priority date (37 CFR 1.492 (e)).		**$0.00**	

CLAIMS	NUMBER FILED	NUMBER EXTRA	RATE		
Total claims	5 - 20 =	0	x $18.00	**$0.00**	
Independent claims	2 - 3 =	0	x $80.00	**$0.00**	
Multiple Dependent Claims **(check if applicable)**			☐	**$0.00**	
TOTAL OF ABOVE CALCULATIONS			=	**$860.00**	
☒ Applicant claims small entity status. (See 37 CFR 1.27). The fees indicated above are reduced by 1/2.				**$430.00**	
SUBTOTAL			=	**$430.00**	
Processing fee of **$130.00** for furnishing the English translation later than ☐ 20 ☐ 30 months from the earliest claimed priority date (37 CFR 1.492 (f)).			+	**$0.00**	
TOTAL NATIONAL FEE			=	**$430.00**	
Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31) **(check if applicable).** ☐				**$0.00**	
TOTAL FEES ENCLOSED			=	**$430.00**	
				Amount to be: refunded	$
				charged	$

a. ☐ A check in the amount of _____ to cover the above fees is enclosed.

b. ☒ Please charge my Deposit Account No. **50-0462** in the amount of **$430.00** to cover the above fees. A duplicate copy of this sheet is enclosed.

c. ☒ The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. **50-0462** A duplicate copy of this sheet is enclosed.

d. ☐ Fees are to be charged to a credit card. **WARNING:** Information on this form may become public. **Credit card information should not be included on this form.** Provide credit card information and authorization on PTO-2038.

NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b)) must be filed and granted to restore the application to pending status.

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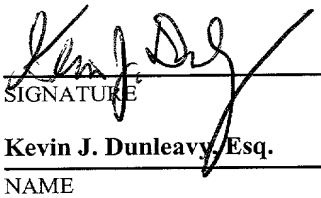

SIGNATURE

Kevin J. Dunleavy, Esq.
NAME

Reg. No. 32,024
REGISTRATION NUMBER

August 16, 2001
DATE

Method and apparatus for determining the cardiac output of a patient

The invention relates to a method for determining the cardiac output of a patient, wherein the patient's respiration cycle is determined and an indicator is injected into the patient's bloodstream over a period of at least substantially one respiration cycle, wherein the change in the indicator value in the bloodstream downstream of the injection point is measured over a period of a number (n) of respiration cycles and the injected amount of indicator is established, wherein the cardiac output is determined on the basis of the measured change in the indicator value, the amount of indicator injected into the blood and the initial value thereof, as well as to an apparatus for determining the cardiac output of the patient.

The measurement carried out in accordance with this method is known as thermal dilution measurement, wherein a catheter is introduced into the patient's bloodstream, via which catheter a relatively cold fluid, for example, is injected into the blood as the indicator. A sensor is attached to the catheter in question or to a similar catheter downstream of the injection point, seen in the direction of flow of the blood, by means of which the blood temperature can be measured. In this manner a so-called thermal dilution curve can be determined, which indicates the change in the temperature. Since the injected amount of indicator is known, it is possible to determine the cardiac output on the basis of the thermal dilution curve. One requirement of the prior art method is that the cardiac output be constant. In practice it has become apparent, however, that two major disruptions of the supposedly constant cardiac output exist; one factor is the pulsating output caused by the action of the heart, and the other factor is formed by all other low-frequency variations in the cardiac output, which are for example caused by artificial respiration of the patient. Generally, the variations in the cardiac output caused by the action of the heart are not considered to have a disruptive effect as regards the application of the thermal dilution

method. When artificial respiration is being applied to a patient by means of an artificial respirator, however, the cardiac output is influenced to such an extent that it can no longer be considered to be constant but to be of a fluctuating nature. It is precisely when artificial respiration is being applied to a patient by means of an artificial respirator that it is highly desirable that the average cardiac output be determined with great accuracy, since this value constitutes one of the criteria in monitoring a patient's condition. Research conducted by J.R.C. Jansen et al, among others, Intensive Care Med 1990, 16, pp. 422 - 425, has shown that when the cardiac output is determined by means of the thermal dilution method, the measuring results may exhibit a dispersion of 65 - 125% of the average.

NL-B-1 005 572 discloses a method and apparatus of the above kind by means of which the accuracy of the thermal dilution method can be enhanced by injecting the indicator exactly over the period of one respiration cycle. By using only one injection over the period of one respiration cycle, the same result is obtained as by computing the average on the basis of a number of thermal dilution measurements according to the conventional method, as for example described in the aforesaid article.

The object of the invention is to further improve the method and apparatus of the kind referred to in the introduction.

In order to accomplish that objective, the method according to the invention is characterized in that a first variation of the indicator value is measured over at least substantially the period of one respiration cycle, preferably directly prior to the injection, and in that the change in the indicator value caused by the injection is determined on the basis of the difference between the change in the indicator value measured over a period of n times that of the first variation and n times the measured first variation.

In this manner the accuracy of the thermal dilution method is further enhanced in that the variation in the indicator value over a period of one respiration cycle is removed from

the measurement of the indicator value over a period of n respiration cycles. As a result, all cyclical variation in the indicator value is removed from the measuring result, so that only the change in the indicator value that is caused by the injection is obtained.

Preferably, a second variation in the indicator value is measured over a period of at least substantially one respiration cycle, preferably directly contiguous to the measurement of the change in the indicator value, wherein the average of the first and the second variation is determined, which average is used for determining the change in the indicator value rather than the first variation. The advantage thus obtained is that the accuracy is further enhanced and that furthermore the slow drift in the indicator value is removed from the measuring result.

According to another embodiment, a so-called pulse contour measurement is carried out as well, whereby an arterial blood pressure signal is measured. The arterial blood pressure signal is approximately proportional to the cardiac output itself, assuming that the characteristic impedance of the vascular system is constant. This requirement is not met in practice, because said characteristic impedance varies with a relatively large time constant. According to the invention an accurate measurement is made possible in that the arterial blood pressure signal is measured, wherein the values of the stroke volume and of the cardiac output over a period of one heartbeat are computed over a period corresponding to the number (n) of respiration cycles, wherein the average of the computed values is determined, and wherein a proportionality constant is computed from a comparison of the average output value thus computed and the cardiac output value determined on the basis of the change in the indicator value, after which the stroke volume and the cardiac output are multiplied by the computed proportionality constant. Thus the result of the thermal dilution measurement is used as calibration for the pulse contour measurement, as it were, after which the cardiac output can be continuously monitored without subsequent injections by means of the pulse contour measurement. The determination of

the cardiac output from the change in the indicator value can be repeated periodically, if desired, by carrying out a new injection and computing the proportionality constant.

The invention also provides an apparatus for determining the cardiac output of a patient, which apparatus comprises a processing unit having a control output for controlling injection means, a first sensor for measuring the change in an indicator value in the patient's bloodstream and a second sensor for determining the patient's respiration cycle, wherein the processing unit is arranged for measuring the change in the indicator value in the bloodstream downstream of the injection point over a number (n) of respiration cycles, establishing the injected amount of indicator and determining the cardiac output on the basis of the measured change in the indicator value, the amount of indicator injected into the blood and the initial value thereof, which apparatus is according to the invention characterized in that the processing unit is arranged for measuring a first variation of the indicator value over at least substantially one respiration cycle, preferably directly prior to the injection of the indicator, and determining the change in the indicator value resulting from the injection on the basis of the difference between the measured change in the indicator value measured over a period of n times that of the first variation and n times the measured first variation.

The invention will be explained in more detail hereafter with reference to the drawing, which schematically shows an exemplary embodiment of the apparatus according to the invention.

Figure 1 is a block diagram of an embodiment of the apparatus according to the invention.

Figures 2 and 3 are diagrams which illustrate the method according to the invention.

It is noted that the term respiration cycle as used within the framework of the description and the claims is understood to mean a natural respiration cycle as well as an artificial respiration cycle. The indicator may be a cold fluid, but also any other suitable indicator, such as a saline solution or a glucose solution or a colouring agent may be used. Although a

cold fluid is used as the indicator in the present embodiment, it is also possible to use another indicator, therefore.

Figure 1 shows apparatus for measuring the cardiac output of a patient, which apparatus comprises a processing unit 1, for example in the form of a PC with suitable software. The processing unit 1 comprises an input/output 2 for controlling injection means 3 (schematically indicated), by means of which a cold fluid can be injected into the patient's bloodstream. To this end a thermal dilution catheter is introduced into the patient's blood vessel in a usual manner. The temperature of said cold fluid is measured by means of a sensor 4, which is connected to processing unit 7. The catheter (not shown) is fitted with a sensor 7 located at some distance from the injection opening, by means of which the temperature of the blood downstream of the injection opening can be measured. Sensor 7 is connected to an input 8 of an amplifier 9, whose output signal is likewise supplied to the processing unit 1. Using the apparatus described so far, a so-called thermal dilution curve can be determined, from which the cardiac output can be computed on the basis of the injected amount of cold fluid and the temperature of said fluid. A plurality of injections of cold fluid would be required in order to be able to determine the average cardiac output. As is disclosed in NL-B-1 005 572, however, it is possible to determine the thermal dilution curve by means of only one injection over the period of one respiration cycle.

To this end the apparatus disclosed herein comprises a sensor 10, which is connected to processing unit 1 via an amplifier 11. Sensor 10 measures a respiration cycle-dependent signal. Such a sensor can for example measure the concentration of carbon dioxide, the strength of the air flow, the temperature of the respiration air or the like. The processing unit 1 now controls the injection means 3 in such a manner that one injection of indicator is carried out accurately for the duration of one respiration cycle and subsequently records the change in the concentration of the indicator for a number n of respiration cycles.

Figure 2 shows a temperature/time diagram wherein the

temperature change is marked off as a function of the time. The average cardiac output is measured by one controlled injection for the duration of a respiration cycle and it is not necessary to carry out a number of measurements. In the example of Figure 2 the period during which the change in the concentration is recorded is indicated T1. This period runs from 6=4 to 6=12.

When a cold fluid is injected as the indicator, the following equation applies:

$$Q_i \rho_i S_i (T_b\ T_i) = Q'_b \rho_b S_b \int \Delta T_b(t) dt$$

wherein Q_i is the injected volume, ρ is the specific heat and S is the specific mass of (i) injected matter and (b) blood, respectively, T is the temperature, Q'_b is the cardiac output and ΔT_b is the change in the temperature of the blood brought about by the injection of cold fluid.

Rearrangement of the formula shows how the cardiac output can be computed.

$$Q'_b = Q_i \frac{\rho_i S_i (T_b T_i)}{\rho_b S_b \int \Delta T_b(t) dt}$$

This formula forms the basis for most thermal dilution "cardiac output" computers.

Research has shown that it is not possible to achieve accurate measuring results in this manner, since the pulsating cardiac output fluctuates due to the natural respiration or artificial respiration via a ventilator. This is schematically shown in Figure 2. In this case the temperature change also includes a temperature variation which is not caused by the injection. This influence on the respiration can be removed by measuring the area below the measured temperature curve over a period of exactly one respiration cycle, preferably directly prior to the injection of the cold fluid. In the embodiment as shown in Figure 2 injection takes place at t=4, and consequently area A is measured first for the duration of period T2. The determination of area B under the temperature

curve is started at the time of injection t=4, and lasts over a period of a number n of respiration cycles until t=12. The area resulting from the injection of the cold fluid will then be Area-Dil = B - n x A.

The cardiac output is then computed as:

$$Q'_b = Q_t \frac{\rho_i S_t (T_b T_t)}{\rho_b S_b \ Area - Dil}$$

The influence of slow temperature drift resulting from an increase or decrease of the body temperature, for example, can furthermore be eliminated by measuring the temperature change over a period of exactly one respiration cycle directly prior to as well as directly contiguous to the injection. This situation is shown in Figure 3. Both area A and area C are thereby measured over period T2 and over period T3, respectively, so that the area resulting from the injection of the cold fluid will then be Area-Dil = B - n/2 x (A + C).

It is therefore possible with the method and apparatus disclosed herein to measure the average cardiac output of a patient with great accuracy by means of only one injection of indicator.

According to a very advantageous embodiment the apparatus is also fitted with a sensor 12, which is connected to the processing unit 1 via an amplifier 13. Sensor 12 measures the arterial blood pressure signal, for example in the aorta. It is known per se that it is possible to compute the noncalibrated value of the stroke volume and the cardiac output from said arterial blood pressure signal over a period of one pulsation of the heart. This is for example disclosed in US-A-3 841 313. In the apparatus disclosed therein, the computed values of the cardiac output are recorded over the period of the measurement of the thermal dilution curve, and the average thereof is determined. Then a proportionality constant is computed by the processing unit 1 by comparing the cardiac output value thus computed with the cardiac output which has been determined by means of the thermal dilution method. Then the computed values

for the stroke volume and the cardiac output resulting from the measurement of the arterial blood pressure can be continuously converted into accurate measurements by means of said proportionality constant.

If desired, the processing unit can be programmed in such a manner that a thermal dilution determination is carried out periodically in the above-described manner, and a new proportionality constant can be determined.

It is noted that the measuring results can be displayed on a screen 14, if desired. Furthermore it is noted that the thermal dilution measurement can be started automatically or by giving a suitable command, for example via a keyboard 15.

The invention is not restricted to the above-described embodiment as shown in the drawing, which can be varied in several ways without departing from the scope of the invention.

CLAIMS

1. A method for determining the cardiac output of a patient, wherein the patient's respiration cycle is determined and an indicator is injected into the patient's bloodstream over a period of at least substantially one respiration cycle, wherein the change in the indicator value in the bloodstream downstream of the injection point is measured over a period of a number (n) of respiration cycles and the injected amount of indicator is established, wherein the cardiac output is determined on the basis of the measured change in the indicator value, the amount of indicator injected into the blood and the initial value thereof, characterized in that a first variation in the indicator value is measured over at least substantially the period of one respiration cycle, preferably directly prior to the injection, and in that the change in the indicator value caused by the injection is determined on the basis of the difference between the change in the indicator value measured over a period of n times that of the first variation and n times the measured first variation.

2. A method according to claim 1, wherein a second variation in the indicator value is measured over a period of at least substantially one respiration cycle, preferably directly contiguous to the measurement of the change in the indicator value, wherein the average of the first and the second variation is determined, which average is used for determining the change in the indicator value rather than the first variation.

3. A method according to claim 1 or 2, wherein the arterial blood pressure signal is measured, wherein the values of the stroke volume and of the cardiac output over a period of one heartbeat are calculated over a period corresponding to the number (n) of respiration cycles, wherein the average of the calculated values is determined, and wherein a proportionality constant is computed from a comparison of the average output value thus calculated and the cardiac output value determined on the basis of the change in the indicator value, after which the stroke volume and the cardiac output are multiplied by the

computed proportionality constant.

4. A method according to claim 3, wherein the determination of the cardiac output from the change in the indicator value is repeated periodically by carrying out a new injection and computing the proportionality constant.

5. Apparatus for determining the cardiac output of a patient, which apparatus comprises a processing unit having a control output for controlling injection means, a first sensor for measuring the change in an indicator value in the patient's bloodstream and a second sensor for determining the patient's respiration cycle, wherein the processing unit is arranged for measuring the change in the indicator value in the bloodstream downstream of the injection point over a number (n) of respiration cycles, establishing the injected amount of indicator and determining the cardiac output on the basis of the measured change in the indicator value, the amount of indicator injected into the blood and the initial value thereof, characterized in that the processing unit is arranged for measuring a first variation of the indicator value over at least substantially one respiration cycle, preferably directly prior to the injection of indicator, and determining the change in the indicator value resulting from the injection on the basis of the difference between the measured change in the indicator value measured over a period of n times that of the first variation and n times the measured first variation.

6. Apparatus according to claim 5, wherein the processing unit is arranged for measuring a second variation in the indicator value is measured over a period of at least substantially one respiration cycle, preferably directly contiguous to the measurement of the change in the indicator value, wherein the processing unit determines the average of the first and the second variation, which average is used for determining the change in the indicator value rather than the first variation.

7. Apparatus according to claim 5 or 6, comprising a third sensor for measuring an arterial blood pressure signal, wherein the processing unit is arranged for calculating the values of the stroke volume and of the cardiac output over a

period of one heartbeat over a period corresponding to the number (n) of respiration cycles, wherein the average of the calculated values is determined, wherein the processing unit compares the average cardiac output value thus calculated and the cardiac output value determined on the basis of the change in the indicator value and computes a proportionality constant, after which the processing unit multiplies the stroke volume and the cardiac output computed from the arterial blood pressure signal by the computed proportionality constant.

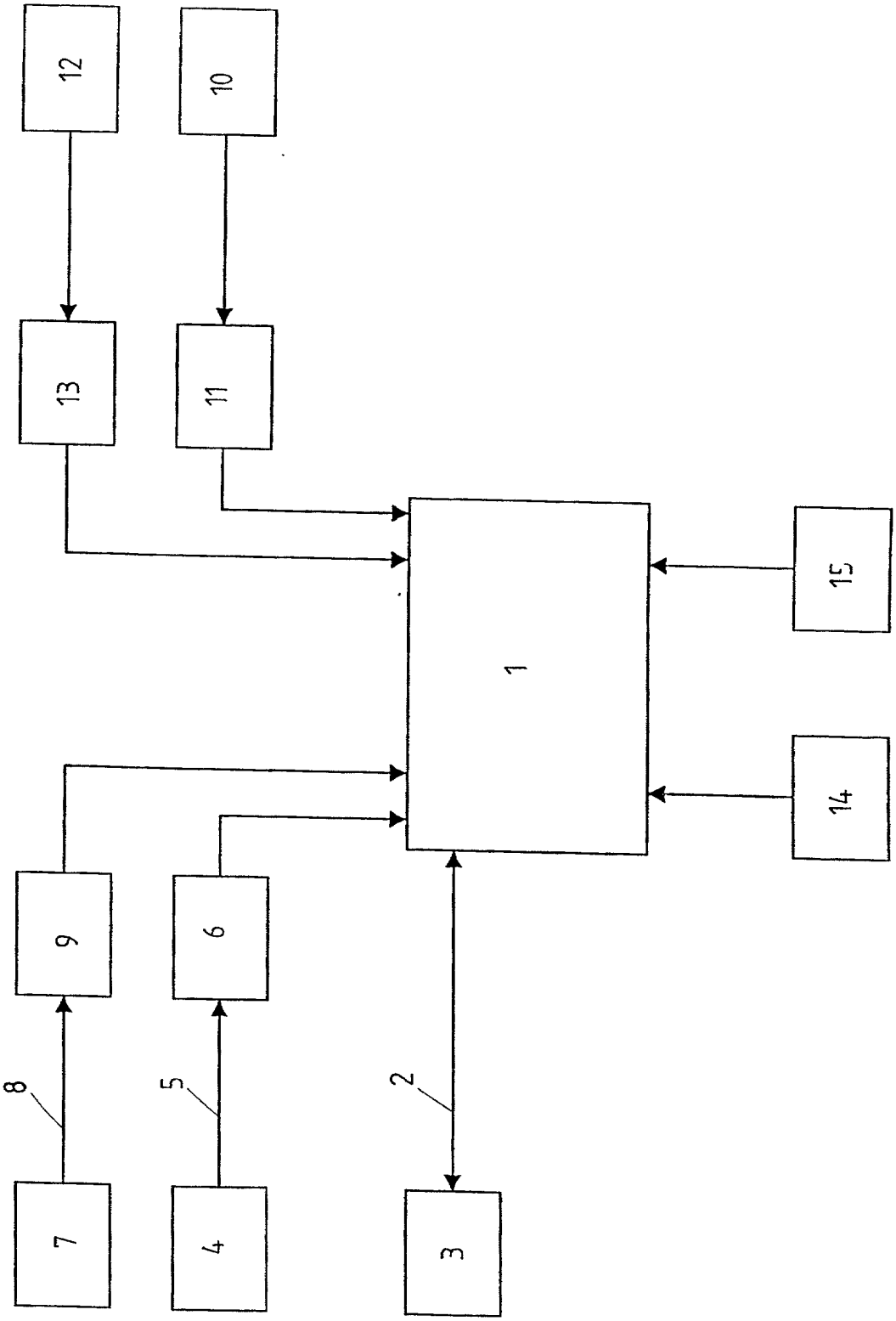

fig.1

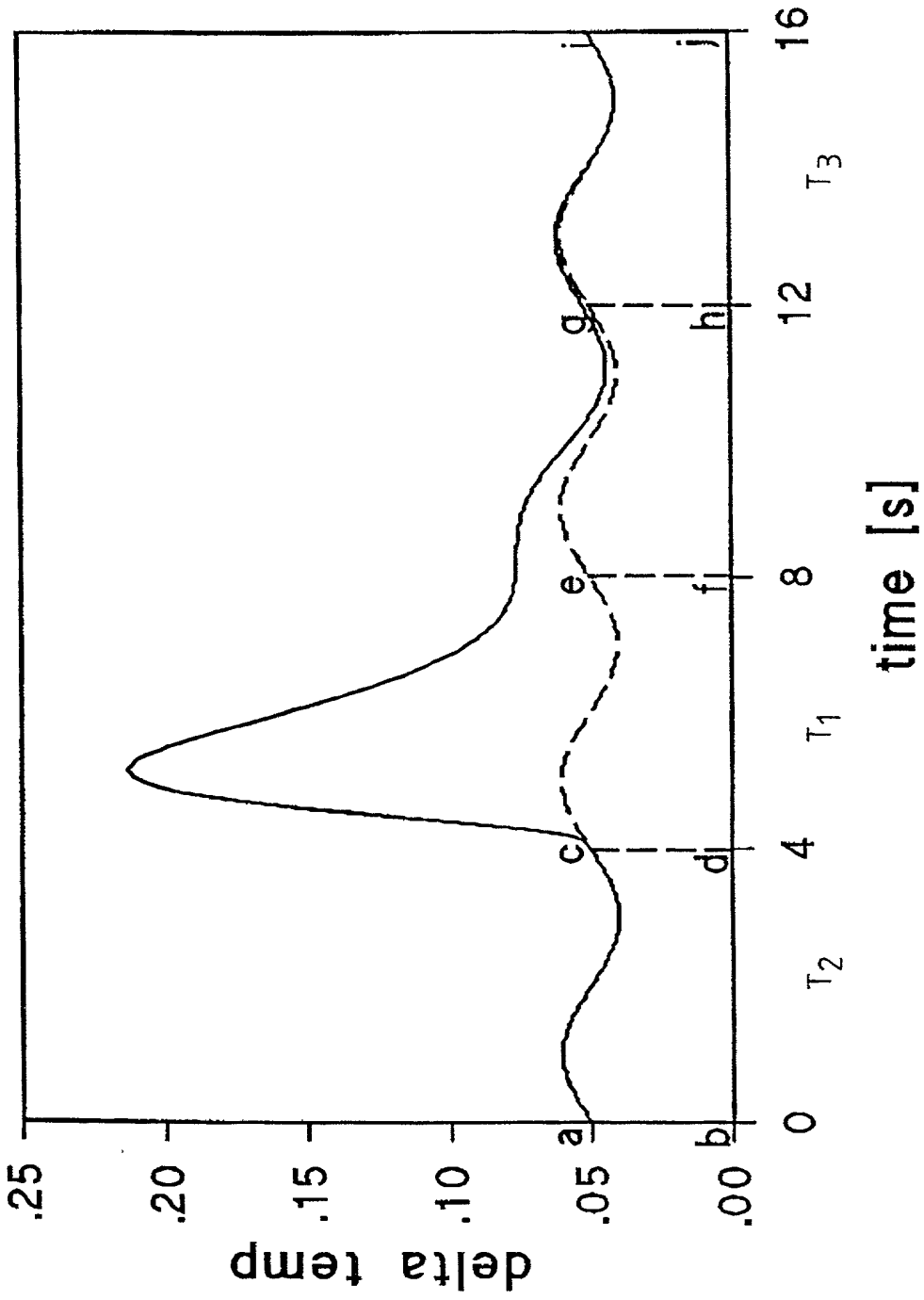

fig.2

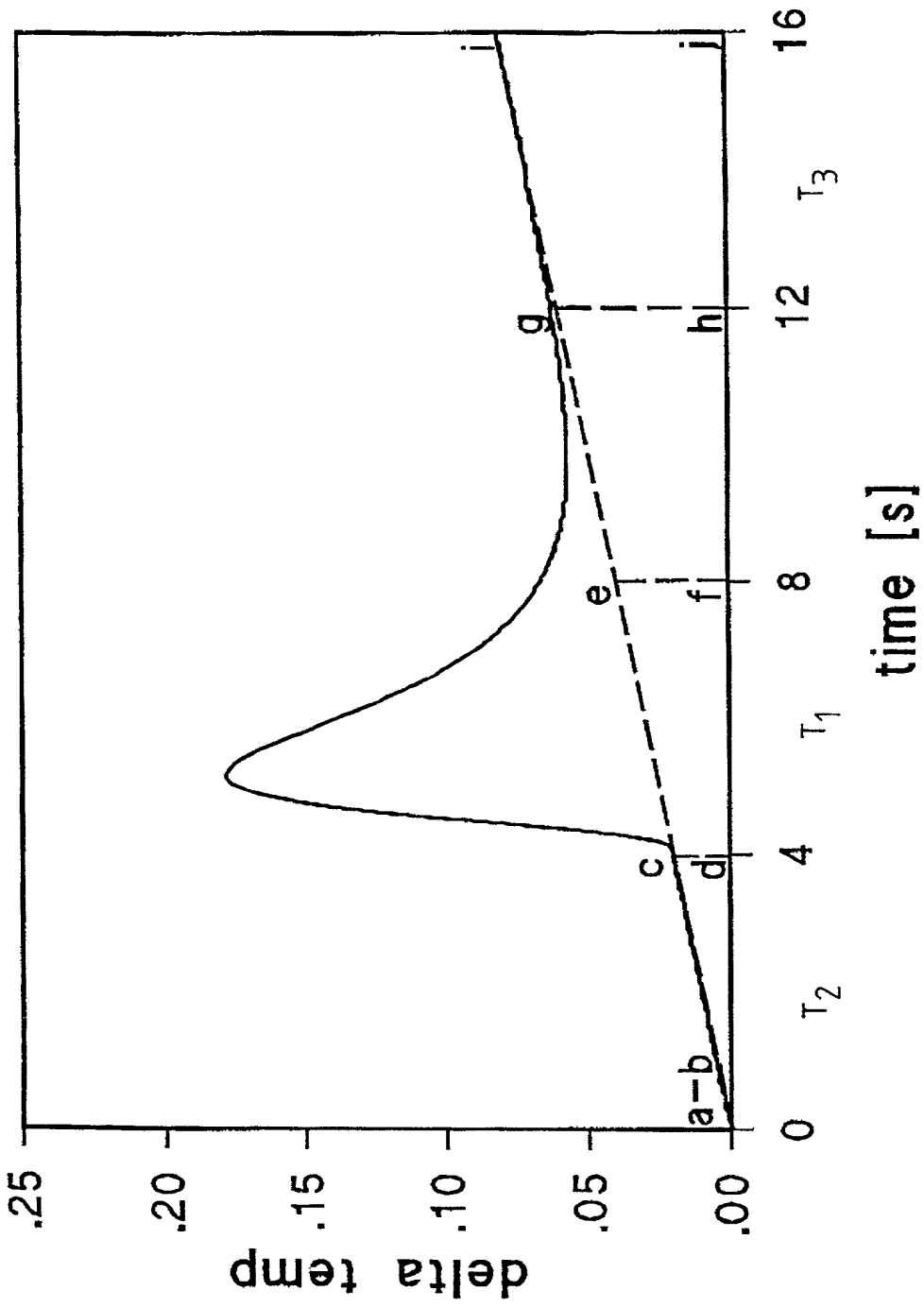

fig.3

Docket No.
DVME-1015US

Declaration and Power of Attorney For Patent Application

English Language Declaration

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name,

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled

METHOD AND APPARATUS FOR DETERMINING THE CARDIAC OUTPUT OF A PATIENT

the specification of which

(check one)

☐ is attached hereto.

☒ was filed on 17 February 2000 as United States Application No. or PCT International Application Number PCT/NL00/00102

and was amended on 7 March 2001
(if applicable)

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose to the United States Patent and Trademark Office all information known to me to be material to patentability as defined in Title 37, Code of Federal Regulations, Section 1.56.

I hereby claim foreign priority benefits under Title 35, United States Code, Section 119(a)-(d) or Section 365(b) of any foreign application(s) for patent or inventor's certificate, or Section 365(a) of any PCT International application which designated at least one country other than the United States, listed below and have also identified below, by checking the box, any foreign application for patent or inventor's certificate or PCT International application having a filing date before that of the application on which priority is claimed.

Prior Foreign Application(s)			Priority Not Claimed
1011339	NETHERLANDS	18.02.99	☐
(Number)	(Country)	(Day/Month/Year Filed)	
			☐
(Number)	(Country)	(Day/Month/Year Filed)	
			☐
(Number)	(Country)	(Day/Month/Year Filed)	

I hereby claim the benefit under 35 U.S.C. Section 119(e) of any United States provisional application(s) listed below:

(Application Serial No.)	(Filing Date)
(Application Serial No.)	(Filing Date)
(Application Serial No.)	(Filing Date)

I hereby claim the benefit under 35 U. S. C. Section 120 of any United States application(s), or Section 365(c) of any PCT International application designating the United States, listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States or PCT International application in the manner provided by the first paragraph of 35 U.S.C. Section 112, I acknowledge the duty to disclose to the United States Patent and Trademark Office all information known to me to be material to patentability as defined in Title 37, C. F. R., Section 1.56 which became available between the filing date of the prior application and the national or PCT International filing date of this application:

(Application Serial No.)	(Filing Date)	(Status) (patented, pending, abandoned)
(Application Serial No.)	(Filing Date)	(Status) (patented, pending, abandoned)
(Application Serial No.)	(Filing Date)	(Status) (patented, pending, abandoned)

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

POWER OF ATTORNEY: As a named inventor, I hereby appoint the following attorney(s) and/or agent(s) to prosecute this application and transact all business in the Patent and Trademark Office connected therewith. *(list name and registration number)*

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Jianzhong Shen-48,076

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Citizenship The Netherlands
Post Office Address Same as above.

Full name of second inventor, if any Johannes Jacobus SCHREUDER
Second inventor's signature Date
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Post Office Address Same as above

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Josef Reinier Cornelis JANSEN

Sole or first inventor's signature — Date

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Second inventor's signature — Date 16/08/01

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